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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,055	03/01/2001	Christian Belmant	BE 8992	6944

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 03/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,055	BELMANT ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *85-89,94-114 and 116-119* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *96-99 and 103-106* is/are allowed.

6)☐ Claim(s) *85-89,95,101,102,107-114 and 116-119* is/are rejected.

7)☐ Claim(s) *94* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 11/17/04.

Claims 90-93, 100, and 115 were canceled and claim 119 was added as requested.

Claims 85-89, 94-114, and 116-119 remain pending and under consideration in this Office Action.

Specification

Applicant's submission of a new Declaration indicating that the specification as submitted on 3/1/01 had been read and understood by the inventors is sufficient to overcome the objection to non-initialed/dated alterations in the specification.

Claim Objections

Applicant's amendments were sufficient to overcome the previous objections to the claims.

Claim 103 is objected to because "ph" should be "pH".

Rejections Withdrawn

Applicant's amendments were sufficient to overcome the rejection of claims 97-114, 116, and 117 under 35 USC 112, second paragraph.

Applicant's amendments were sufficient to overcome the rejection of claims 97-114 under 35 USC 112, first paragraph for lack written description.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Applicant is advised that should claim 85 be found allowable, claim 119 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement

Claims 85-89, 95, 101, 102, 104, 107-114, 118 and 119 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro

methods of activating Tγ9δ2 lymphocytes, does not reasonably provide enablement for activating Tγ9δ2 lymphocytes in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In ex parte Forman, 230 USPQ 546 (bd. App. 1986) the board considered the issue of enablement in molecular biology and considered several factors.

Nature of the invention and Breadth of the claims

Claims 85-89, 95, 107-114, 118 and 119 are broadly drawn to methods of activating Tγ9δ2 lymphocytes, in vitro or in vivo. The specification teaches that Tγ9δ2 lymphocytes may be activated in vitro for the purpose of studying the activated cells. See page 20, lines 1-6. When used in vivo, the method may be for therapeutic use (page 20, lines 6 and 7) or for diagnostic use (page 20, lines 29-32). The scope of therapeutic uses is broad and embraces both preventative and curative embodiments (page 20, lines 29-32). The scope of treatable diseases includes conditions belonging to the group comprising cancers, infectious diseases, in particular mycobacterial infections (leprosy, tuberculosis etc.), parasitic conditions (malaria etc.), and pathological immunodeficiency syndromes (MDS etc.) The specification also teaches that Tγ9δ2 cells can be activated ex vivo and then used for therapy. Use activated T-cells for therapy is known in the art as adoptive immunotherapy.

State of the prior art

Yamaguchi et al (J. Immunol. Met. 205(1): 19-28, 6/23/97) taught that gamma delta T cells make up no more than 10% of peripheral blood mononuclear cells, but

appear to play an important role in host defense against tumor growth. In order to evaluate their functional activity against tumors, large quantities of cells are required. Yamaguchi taught a method of producing large quantities of gamma delta T cells by isolating them inducing TCR/CD3-mediated signal transduction by contacting the cells with an anti-CD3 antibody and IL-2. Yamaguchi noted that this method may make it possible to produce sufficient numbers of gamma delta T cells for clinical trials of anti-tumor adoptive immunotherapy. See abstract. Thus it was recognized in the art at the time of the invention that obtaining a sufficient number of gamma delta T cells was an obstacle to adoptive immunotherapeutic methods relying on these cells. Although Yamaguchi taught a potential solution to this problem, it was clear that those of skill in the art would not be convinced that the teachings of Yamaguchi were sufficient to solve the problem. For example, Janssen et al (J. Immunol. 146(1): 35-39, 1/1/91) taught that stimulation of gamma delta cells with anti-CD3 antibody and IL-2 led ultimately to cell death through apoptosis, thus calling into question the usefulness of this method for expanding gamma delta cells to the numbers needed for therapeutic purposes. Indeed Lopez et al (Blood 96(12): 3827-3837, 12/1/2000) taught that the exploitation of gamma delta T cells for therapeutic ends remained largely unrealized because of the extreme difficulty in obtaining sufficient quantities of these cells. Lopez noted that while treatment of gamma delta T cells with anti-CD3 or anti-TCR antibodies is an attractive means of expanding these cells, this method results in apoptosis, thereby presenting a serious obstacle to developing approaches to incorporate gamma delta T cells into any form of adoptive immunotherapy. See page 3827, column 2, lines 2-18. Lopez

concluded, [w]hether γδ-T cells have therapeutically exploitable biologic properties such as antiviral, antitumor, or hematopoietic stem cell graft-facilitating effects, remains to be determined. See page 3836, column 2, lines 5-8. Lopez indicates that amounts of cells far in excess of 10^9 would be needed for therapeutic purposes. See page 3836, lines 7-17.

A search of the prior art revealed no instances of complete disease prevention or cure through the use of Tγ9δ2 cell adoptive immunotherapy.

Unpredictability in the art

The teachings of Janssen (1991) and Lopez (2000) above show that at the time of the invention, the art of adoptive immunotherapy using Tγ9δ2 cells was highly unpredictable, essentially because of the technical difficulty in obtaining sufficient numbers of apoptosis-resistant cells. Furthermore, even if a sufficient number of cells could be obtained, it was not predictable that these cells would be useful for any therapeutic method. See page 3836, column 2, lines 5-8.

Guidance and exemplification in the specification

The specification teaches how to make phosphoepoxide compounds and demonstrates that they can be used to stimulate proliferation of Tγ9δ2 cells in the presence of IL2. See e.g. pages 25-33 of the specification. The specification fails to teach the production of quantities of Tγ9δ2 cells approaching 10^9, and fails to provide any information as to the mechanism of Tγ9δ2 cell proliferation, or any apoptotic effects of phosphoepoxide-mediated mitogenesis. The specification provides no working

example of any therapeutic use of the clamed methods. The specification also provides no guidance as to how to use the claimed methods for any in vivo diagnostic purpose.

Amount of experimentation required

Due to the unpredictable nature of the art of Tγ9δ2 cell adoptive immunotherapy, the recognition in the art that larger numbers of Tγ9δ2 cells were required for therapy than could be produced by existing methods, the failure of the specification to teach how to produce sufficient numbers of cells for therapeutic purposes, and whether or not these cells are subject to apoptosis, particularly in view of their treatment with IL2, one of skill in the art would have to perform undue experimentation to use the claimed compositions for therapeutic purposes as required by the claims. In addition, although the specification teaches that the claimed methods may be used in vivo for diagnostic purposes, the specification gives no guidance or examples in this regard, and it is not immediately apparent how one could use the claimed methods for diagnostic purposes in vivo. This rejection can be overcome by limiting the claimed methods to the scope of in vitro. Claims 101 and 102 are included in this rejection because they are compositions which are adapted to be used in vivo. Claim 104 is included because it is a composition intended to be applied topically, and the specification recites no use for such a composition other than in vivo.

Response to Arguments

Applicant's arguments filed 11/17/04 have been fully considered but are unpersuasive.

Applicant responds to the rejection at pages 22-26 of the response. In essence, Applicant argues that the rejected claims are not drawn to any method of adoptive immunotherapy, but concern instead an in vivo use of the invented compounds. Applicant asserts that the compounds are to be directly administered to patients in vivo with the result that Tγ9δ2 lymphocytes are activated in vivo. Even though the Office has established that therapeutic ex vivo stimulation of gamma delta T cells for therapeutic use (adoptive immunotherapy) is highly unpredictable, Applicant concludes that the Examiner has failed to meet the burden of demonstrating that the specification is not enabled for in vivo use of the invented compounds. This argument is unpersuasive because, as Applicant asserts, the intended in vivo use of the invention is for therapeutic activation of Tγ9δ2 lymphocytes. As such, the claimed method is subject to at least the same level of unpredictability established for the ex vivo method of adoptive immunotherapy, as well as the increased unpredictability attending the direct administration of the compositions to non-isolated cells in vivo. By comparison to adoptive immunotherapy, this in vivo approach is even more unpredictable because of factors such as the unknown effects on the claimed compounds of in vivo metabolism, and the unknown effects of dilution of the compounds relative the ex vivo system. Applicant argues that the art relied upon by the Examiner to formulate the prima facie case for lack of enablement is not pertinent to the claimed method. However, this is unpersuasive because the cited art is analogous in that it concerns the activation of gamma delta T cells. The fact that the cited art concerns a simpler ex vivo system does not detract from its relevance to the more complex in vivo system in which it is

unknown how many Tγ9δ2 lymphocytes will be contacted with the compounds, and unclear what are the effects of the in vivo environment on the stability and activity of the compounds.

Note that claims 85-89 and 95 stand rejected even though Applicant has amended these claims to recite a "method for activating a Tγ9δ2 lymphocyte in vitro. This is because it is not clear from the method steps that the activation step of the method takes place in vitro. The claims could be read to embrace a method wherein the phosphoepoxide is administered in vivo, and then cells are isolated and allowed to proliferate in vitro. It is suggested that the term "in vitro" should be inserted directly after the term "contacting". Note that should this be done, claim 94 would not further limit claim 88. Also note that this amendment would render claim 95 indefinite/unenabled because claim 95 requires topical administration. This implies delivery in vivo, not in vitro.

Conclusion

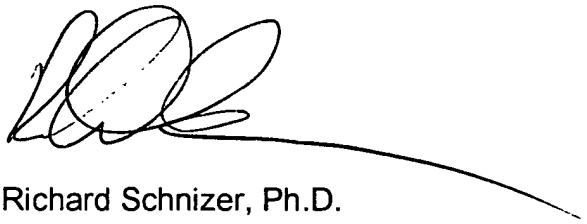
Claims 96-99 and 101-106 are allowable.

Claim 94 is objected to because it depends from a rejected claim, but would be allowable if rewritten, incorporating all the limitations of the claims from which it depends. Alternatively, it is suggested that claim 94 should be canceled, and claim 85 should be amended to require contacting Tγ9δ2 lymphocyte with the claimed phosphoepoxides in vitro, as discussed above.

All claims are free of the prior art of record.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.



Richard Schnizer, Ph.D.